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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,856	12/04/2003	Manne Satyanarayana Reddy	BULK 3.0-034	8301

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EXAMINER	
GRAZIER, NYEEMAH	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,856	REDDY ET AL.	
	Examiner	Art Unit	
	Nyeemah Grazier	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *8-16 and 24-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,17,18 and 20-22* is/are rejected.

7)☒ Claim(s) *3,7,19 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

FIRST ACTION ON THE MERITS

I. ACTION SUMMARY

Claims 1-88 are currently pending. Claims 8-16, and 24-34-88 withdrawn from further consideration by the Examiner because said claims are drawn to a non-elected invention. 37 C.F.R. § 1.142(b).

II. PRIORITY

This application claims benefit of priority under 35 U.S.C. 119 (a-d) to foreign application INDIA 908/MAS/2002, filed December 4, 2002.

III. INFORMATION DISCLOSURE STATEMENT

The information disclosure statement (IDS) submitted on July 19, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner has considered the information disclosure statement.

IV. RESTRICTION/ELECTION

A. Election: Applicant's Response

Applicant's election of Group I, claims 1-7 and 17-23 in the response filed on January 3, 2007 is acknowledged. The applicant traverses the restriction on the grounds that the restriction is improper because the inventions are neither independent nor distinct and therefore would not impose a burden on the Examiner.

The traversal was persuasive in-part. Namely, Groups II (claims 8-12) and Group IV (claims 24-28) will be examined together and Groups VII (claims 49-55) and IX (claims 76-82) will be examined together as Applicant's arguments were persuasive.

However the restriction between Group I, claims 1-7, 17-23 and Group II, claims 8-12 and 24-28 and between Groups VII and Group IX are distinct as stated in the previous action. The inventions are distinct because the process for preparing crystalline/amorphous cetirizine dihydrochloride may be prepared by a process that is materially distinct from the instant invention. See, e.g., US 6,908,999B2. The restriction as to the other groups are FINAL.

V. REJECTION(S)

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 17, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by *Cossement et al.*, GB 2,225,321 A ("the '321 publication"). The '321 patent teaches the compound and the process of making levorotatory and dextrorotatory dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride. See, e.g., p. 8., lines 3-5; p. 9, ll. 20-39; p. 10, ll. 15-27.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 22 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification is silent as to make and use a thermodynamically stable form of the pharmaceutical composition comprising a "crystalline form" of the product having utility at room temperature for said compositions. It is recognized in the art that only one crystalline form of a product is thermodynamically stable at any given temperature and pressure. (See, U.S. Pharmacopia).

There is a lack of description as to whether the compositions are able to maintain the compound in the crystalline forms as claimed. Processing a compound into a pharmaceutical composition could create a different form that the crystalline form being claimed or even back to the compound itself. See, Habeblian, pp. 912-913. Doelker et al, Abstract, "one may also obseve changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or dosage form." See also, Taday et al., p. 831 "Once in the desired crystalline form, the polymorphic form may be changed by incorrect storage or even during the tablet preparation." See also, id. at 836, figure 8 (showing the compound Form 4 in the pharmaceutical composition resulted in similar spectra. In the instant case, the specification fails to describe the pharmaceutical compositions claimed in terms of their X-ray diffraction pattern or infrared spectrum data. Verily, the specification discloses a preferred embodiment wherein the composition includes a small amount of crystalline cetirizine dihydrochloride (about 1%) and 80% of the crystalline form. *See*, Specification, p. 12, ¶ [0053].

Chemical & Engineering News suggests that formulation of drugs or pharmaceuticals in its metastable forms, for example, on polymorph, is highly unpredictable. The metastable forms will disappear and change into the most thermodynamically stable form. Muzaffar et al., p. 60 (stating "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form.") and p. 63-65 (stating that pharmaceutical preparation processes affect polymorphism).

Thus, the specification lacks description of how the pharmaceutical compositions can be prepared in order to maintain the particular crystalline compound having a specific infrared spectra and X-ray diffraction being claimed. Disclosure does not describe the X-ray diffraction patterns for pharmaceutical compositions comprising the crystalline forms. The disclosed X-ray diffractions and infared spectra supports only the crystalline forms of levorotatory and dextrorotatory

dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride.

35 U.S.C. §112, 1st Paragraph - Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific disclosed crystalline forms of levorotatory and dextrorotatory dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride, the disclosure is not enabling pharmaceutical compositions comprising said crystalline forms of levorotatory and dextrorotatory dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride. Additionally, the specification is not enabling for the term "a prophylactically" in the recitation for the pharmaceutical composition.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The relevant factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been set forth in *In re* Wands. See *In re* Wands, 8 USPQ.2d 1400 (1988). The factors are as follows:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. In re Fouche, 169 USPQ 429 (CCPA 1971). *See also*, MPEP 716.02(b).

Nature of the Invention

The nature of the invention is the crystalline forms of levorotatory and dextrorotatory dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride, pharmaceutical compositions of said products, the preparation of said products, and the method of using same.

State of the Prior Art

Polymorphs can convert from one form to another during the manufacturing process of a pharmaceutical drug. *See*, Chemical Engineering News, p. 32.Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. *Id.* at 33.Although identical in chemical compositions, crystalline forms can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. Polymorphs tend to convert from less stable to more stable forms. No method exists to predict the polymorphs of a solid compound with any significant certainty. In drug design, it is best to work with the most stable polymorph to avoid conversions to other polymorphs. However, the most stable polymorph is normally the least soluble. To improve bioavailability, drug companies trade off polymorph stability with solubility, metastable forms.

Amount of Direction/Guidance and the Presence or Absence of Working Examples

The specification discloses x-ray diffraction patterns of crystalline forms of levorotatory and dextrorotatory dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride. *See*, Specification, Table I, pp. 13-14; See also, Figures 1 and 2. The specification teaches that the percent composition of crystalline dextrorotatory cetirizine dihydrochloride salt can be determined indirectly by comparing the x-ray powder diffraction and their relative intensities of the peaks from the diffraction pattern of the unknown composition with a calibration curve derived from the X-ray diffraction patterns of a

pure crystalline sample of dextrorotatory cetirizine dihydrochloride salt. *See*, Specification, p. 14. Polymorphs often change into other forms during drug manufacture into a pharmaceutical composition. Based on the unpredictability in the art, the specification is not enabling for pharmaceutical composition comprising crystalline forms of levorotatory and dextrorotatory dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride.

The Breadth of the Claims

The breadth of the claims are drawn to pharmaceutical compositions comprising crystalline forms levorotatory and dextrorotatory dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride.

The Quantity of Experimentation Needed

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification. Specifically, there is no guidance regarding the stability of the pharmaceutical composition comprising the crystalline forms, and there is no guidance as to the x-ray powder diffractions of the composition itself. Thus, in consideration of the pertinent factors above, the specification is not enabled for the inventions of claims 6 and 22.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 5, 18, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The expressions "substantially" and "about" in said claims have indefinite meanings and therefore the claims fail to particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

Furthermore claims 2 and 18 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

The second paragraph of 35 U.S.C. 112 requires that the claim particularly point out the invention. Claims may not refer to the Specification. Verily, claims that refer to the specification are improper. See Ex parte Fressola, 27 USPQ.2d 1608 (BPAI 1993). Claim 2 and 18 improperly refers to the Specification (e.g. FIG. 1, FIG. 2).

The abovementioned objection under 35 U.S.C. § 112, 2nd will be obviated by the following suggestions: inserting the figure into the claim.

VI. OBJECTION(S)

Claims 1-7, and 17-23 are objected to because said claims refer to the invention by nomenclature and also by the name "cetirizine." Additional, some or all of the above mentioned claims include both names when identifying the one product. It is suggested that the Applicant delete "cetirizine" and refer to the invention by nomenclature.

Claims 3, 7, 19, and 23 are objected to because said claims depend from rejected based claims.

VII. CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nyeemah Grazier whose telephone number is (571) 272-8781. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:30 a.m. - 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571) 272 - 0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Very truly yours,

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